the elevation in $P_a$, the fall in CO and the increase in $P_a$
following E coli infusion in goats. In addition, TxA4 significantly contributes to edema formation, perhaps by direct effects on permeability, but more likely by elevation of pulmonary microvascular pressures.

Role of Thromboxane in the Pulmonary Response to Pulmonary Microembolization

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Pulmonary microembolism is associated with the generation of prostaglandin thromboxanes. Since pulmonary microembolism also causes lung edema, the generation of these arachidonic acid products may contribute to extravascular fluid accumulation in the lung. Thromboxane A4 (TxA4) is a particularly vasoactive substance in the pulmonary circulation since infusion of the cyclic endoperoxide analog (U-46619), which is reportedly a TxA4 mimic, increased net transvascular fluid filtration in the lung (i.e., pulmonary lymph flow). The increase in fluid filtration was mediated by increase in the pulmonary microvascular hydrostatic pressure because the increase in pulmonary lymph flow was associated with a decrease in the lymph-to-plasma protein concentration ratio, a response that is characteristic of an increase in the microvascular hydrostatic pressure. In addition to the hemodynamic effect of TxA4, TxA4 also interacts

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FIGURE 1. Effects of thrombin on leukocyte and platelet counts in control sheep and in sheep pretreated with the thromboxane synthetase inhibitor UK-37,248.

FIGURE 2. Changes in pulmonary hemodynamics in the control thrombin group and the group treated with UK-37,248.

with leukocytes by promoting their adherence in the fibrin matrix. This interaction may be of considerable importance in the development of lung vascular injury after pulmonary microembolization and the associated secondary thrombosis because the injury is dependent upon the presence of granulocytes.

In the present study, we examined the role of TxA4 generation in mediating the lung vascular injury after pulmo-
formed pulmonary embolization with thrombin because this causes intravascular coagulation and pulmonary microvessels become embolized with fibrin and formed elements (platelets and leukocytes). The role of TxA₄ in mediating the increase in lung vascular permeability after thrombin-induced pulmonary microembolization was examined by using the new thromboxane synthetase inhibitor UK-37,248 (obtained from Pfizer Labs). Sheep were pretreated with a 10 mg/kg injection of the drug followed by infusion of 3 mg/kg/hr for 3 or 4 hr. The pulmonary lymph flow and pulmonary hemodynamic parameters were monitored before and after a 15 min infusion of thrombin (60-70 units/kg). The results of the sheep pretreated with UK-37,248 were compared to control animals.

The changes in the counts of leukocytes and platelets are indicated in Figure 1. The leukocyte decreased steadily after the thrombin infusion in the control group, whereas the count decreased transiently in the sheep pretreated with the UK-37,248. However, the platelet count decreased similarly in both groups. The hemodynamic parameters are shown in Figure 2. The pulmonary arterial pressure and pulmonary vascular resistance increased after the thrombin infusion in the control group indicating pulmonary embolization secondary to intravascular coagulation, but then both pressure and resistance decreased steadily during the experiment. The left atrial pressure and pulmonary blood flow did not change significantly from baseline in either group. In contrast to the control group, there were steady increases in pulmonary arterial pressure and in pulmonary vascular resistance after thrombin in the UK-37,248-treated animals. The pulmonary lymph data are shown in Figure 3. The pulmonary lymph flow and transvascular protein clearance (lymph-to-plasma protein concentration ratio × lymph flow) increased in the control group within 30 min after thrombin infusion and these increases were sustained for the duration of the study. The lymph-to-plasma protein concentration ratio was also increased from baseline at 135 and 150 min following embolization. In contrast, pulmonary lymph flow increased in the group pretreated with UK-37,248 only at 150 min postembolization while the transvascular protein clearance did not change significantly from baseline because of the decrease in the lymph-to-plasma protein concentration ratio.

Therefore, the results indicate that thrombin in the control group caused a progressive decrease in the white blood cell count, suggesting margination of these cells in the microcirculation. However, this process was a short-lived one in the animals pretreated with UK-37,248 suggesting that TxA₄ generation contributes to the time-dependent decrease in the leukocyte count after thrombin-induced pulmonary microembolization. This is in accord with previous studies which implicate a role of TxA₄ in mediating leukocyte adherence and aggregation. The present study suggests that TxA₄ generation is required for the decrease in the leukocyte count because the decrease did not occur when thromboxane-synthetase was inhibited. The platelet count decreased similarly in both groups probably because thrombin directly activates the platelet aggregation and this process does not require TxA₄ generation. The increases in pulmonary artery pressure and pulmonary vascular resistance were not sustained in the control group after thrombin which may be the result of generation of a pulmonary vasodilator substance (eg, PGI₂), decreased production of a pulmonary vasoconstrictor substance (eg, TXA₄), or recanalization of vessels as a result of fibrinolysis.

Thrombin infusion produced increases in pulmonary lymph flow, transvascular protein clearance and lymph-to-plasma protein concentration ratio, indicating an increase in the permeability of pulmonary microvessels to proteins. However, the treatment with UK-37,248 prevented these increases suggesting that TxA₄ also contributed to the mediation of a thrombin-induced lung vascular injury. The mecha-

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**Figure 3.** Changes in pulmonary lymph flow, lymph-to-plasma protein concentration ratio, and transvascular protein clearance after thrombin in the control group and in the UK-37,248 treated group.
nism of this observation may be related to the observation that leukopenia was transient in the animals pretreated with the thromboxane synthetase inhibitor (Fig 1); therefore, TxA₂ may contribute to lung vascular injury after pulmonary microembolization by increasing leukocyte adherence and margination in the pulmonary microvessels. The other possibility is that there is increased generation of PGI₂ after thrombin-induced pulmonary microembolization when thromboxane synthetase is inhibited. The increased PGI₂ generation may have leukocyte disaggregating effect and thus prevent the thrombin-induced lung vascular injury.

REFERENCES

Platelet-Induced Pulmonary Hypertension and Edema*

A Mechanism Involving Acetyl Glyceryl Ether Phosphorylcholine and Thromboxane A₂

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Intrapulmonary platelet sequestration is a common feature of the adult respiratory distress syndrome (ARDS), but the specific contribution of platelets to ARDS is unknown. Further interest in the role of platelets in the pathogenesis of ARDS is stimulated by the elucidation of platelet activating factor (acetyl glyceryl ether phosphorylcholine—AGEPC). This naturally-occurring phospholipid is secreted by human alveolar macrophages and neutrophils, causes platelets to release vasoactive substances, and generates pulmonary hypertension and respiratory distress when infused intravenously into rabbits.

On the basis of the foregoing, we hypothesized that stimulated macrophages and neutrophils release AGEPC which causes platelets to release vasoactive factors, such as thromboxane A₂ (TxA₂), which subsequently cause pulmo-

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HYPOTHESIS
ROLE OF PLATELETS AND PAF IN ARDS

Alveolar macrophages and neutrophils secrete PAF causing
platelet accumulation and release of TxA₂ and other factors which cause
pulmonary hypertension and edema.


METHODS

Heart-lung preparations were excised from anesthetized New Zealand white rabbits and suspended from a weight transducer. The pulmonary artery and left ventricle were cannulated and perfused with a 3% albumin-salt solution. A pressure transducer monitored mean pulmonary artery pressures. The lungs were perfused for 55 min while various agents with platelets were infused and the lungs were observed for weight and pressure changes. At the end of the study, the right lung was lavaged with 20 ml of saline solution, and albumin concentrations were assayed.

In initial studies, human platelet-rich plasma (4.3±0.3×10⁶ platelets, PRP) was infused 20 min into the experiments followed 5 min later by AGEPC (20 μg). Control studies were done by infusing either platelet alone (at 20 min), AGEPC alone (at 25 min), or platelet-poor plasma (5.0±0.3×10⁶ platelets in 10 ml plasma) plus AGEPC. Purified neutrophils (2.4±0.3×10⁶ cells in 10 ml of HBSS) were also infused in some experiments at 20 min followed by 25 min by AGEPC (20 μg).

Pressure control studies were done by infusing platelets and AGEPC followed by nitroglycerin lactose (NTG) to maintain low perfusion pressures. After 55 min of perfusion, the left atrial pressure was raised by 10 mm Hg for 10 min after which the lungs were observed for an additional 5 min (total perfusion time was 70 min).

Additional studies examined the effects of TxA₂ in the lung system. Platelets were incubated with imidazole (50 μg/ml), a TxA₂ synthetase inhibitor, before infusion with AGEPC. Other studies utilized 13-azaprostanoid acid (13-APA), a TxA₂ receptor site blocker, which was infused into the lung system before infusion of platelets and AGEPC. In selected studies, TXB₂, the stable metabolite of TxA₂, was measured in perfusates by radioimmunoassay methods.

RESULTS

Lungs perfused with platelet-rich plasma (PRP) and AGEPC developed increased pulmonary artery pressures, weights and lavage albumin concentrations compared to lungs infused with platelets alone, AGEPC alone, platelet-poor plasma (PPP) plus AGEPC, or neutrophils plus AGEPC (Table I). If low perfusion pressures were maintained by the